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Efficient synthesis of D-*xylo* and D-*ribo*-phytosphingosines from methyl 2-amino-2-deoxy-β-D-hexopyranosides

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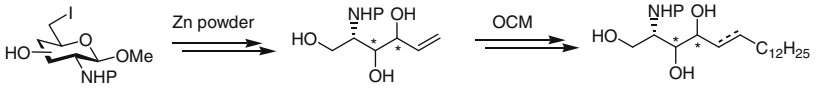
ABSTRACT

A general and flexible synthetic approach to biologically important 5,6-unsaturated C_{18}-phytosphingosines was developed via olefin cross-metathesis employing truncated C_6-phytosphingosines as the key intermediates. These were efficiently prepared in high yields by zinc-mediated reductive opening of methyl 2-amino-2-deoxy-β-hexopyranosides.



1. Introduction

Phytosphingosines are important structural constituents of cell membranes (Fig. 1).[1] Unlike sphingosines which are abundant in animals, phytosphingosines are mainly found in plants but are also present in some bacteria, fungi, and marine organisms.[2] Although the majority of phytosphingosines have a C_{18} lipid chain, C_{20}-phytosphingosines may also exist depending on the source of origin; all possess a saturated lipid chain. Interestingly, an unsaturated analog, Amphicerebroside F (**2**, Fig. 1), which has a trans double bond at C-5 and a terminal isopropyl group, was isolated from the marine organism *Amphimedon viridis*.[3] Studies have shown that phytosphingosines play important structural and regulatory roles in living organisms, and some glycolipids containing unsaturated phytosphingosine analogs exhibit antifungal activity.[2,3] For example, D-*ribo*-phytosphingosine was reported to be a potential heat-stress signal in yeast cells,[4] and some of its glycosylated forms, such as KRN7000,[5] exhibit potent immunostimulatory properties capable of activating natural killer T (NKT) cells to produce a spectrum of cytokines. KRN7000 is a synthetic analog containing a D-*ribo*-C_{18}-phytosphingosine and is related to agelasphin, which was isolated from a marine sponge.[6,7]

The biological significance of phytosphingosines has prompted considerable interest in the synthesis of this class of compounds and their analogs.[8] However, many reported syntheses suffer from inefficiency and lack the flexibility to access other stereoisomers or alkyl chain lengths.[9] Recently, a number of groups have synthesized bioactive sphingosines via olefin cross-metathesis (OCM) using different truncated precursors,[10,11] and in the case of phytosphingosines, three similar approaches were also reported.[12] Here we report our strategy to synthesize some truncated C_6-phytosphingosines and their subsequent transformation to 5,6-unsaturated C_{18}-phytosphingosines using Grubbs' catalyst-mediated OCM. The success of our approach is demonstrated by the synthesis of two families of phytosphingosines with either D-*xylo* or D-*ribo* configurations. All C_6-phytosphingosines have a terminal alkene

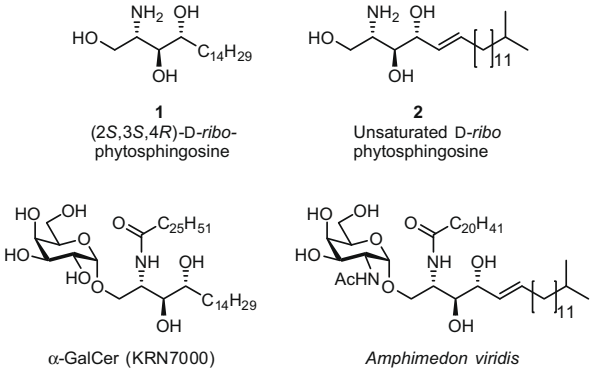


Figure 1. Phytosphingosines and their glycoceramides.

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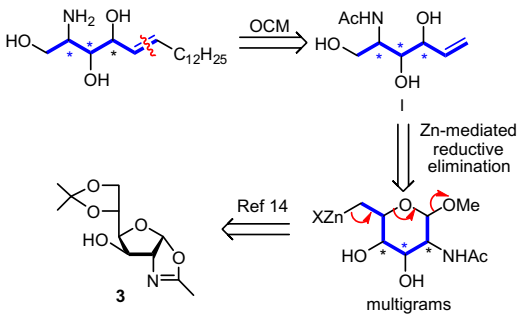
functional group which permits further chemical derivatization and conjugation to provide bioconjugates of the type that we have previously reported.[13]

2. Results and discussion

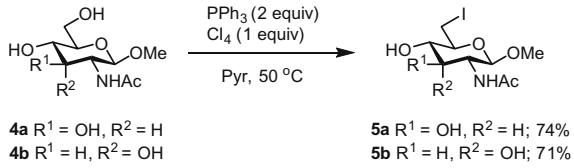
The retrosynthesis is illustrated in Scheme 1. The 5,6-unsaturated C_{18}-phytosphingosines were prepared from truncated C_6-amino alcohols **I** with a terminal double bond that can be used for OCM reaction with a suitable alkene. The backbone of **I** can be obtained from the parent 6-halogenated 2-acetamido-2-deoxy-hexoside via zinc-mediated reductive ring-opening;[14] the double bond of structure **I** originates from the C-5 and C-6 carbon atoms, while the primary hydroxymethyl group is generated from the aldehyde at C-1. The stereocenters of **I** that define different truncated phytosphingosines are directly inherited from the parent *gluco*-, *galacto*-, *allo*-, or *gulo*-aminohexoses, all of which can be obtained on large scales after 1–3-step transformations from the inexpensive methyl 2-acetamido-2-deoxy-β-D-glucopyranoside, which was in turn prepared from the key oxazoline **3** on a 30-g scale, as reported by our group.[15] Although there are two published syntheses of D-*ribo*-C_{18}-phytosphingosine from D-glucosamine via a Wittig olefination[8a,16] or a stereocontrolled alkylation;[17] both suffered from long reaction sequences and required separation of diastereoisomers. In principle, both α- and β-glycosides of amino sugars can be used to obtain the desired intermediates **I**; however, our initial investigation[18] indicated that the use of β-glycosides should be a preferred choice because of their higher reactivity in the zinc-mediated elimination step compared to the reactivity of the corresponding α-anomers. We attributed the higher reactivity of β-anomers to the favorable antiperiplanar orientation of the C-5–O-5 and C-1-OMe bonds (the higher reactivity of β-glycosides in reductive elimination was observed when treating an α/β-mixture of GlcNAc glycosides with preactivated Zn powder).

The synthesis of truncated D-*xylo*- and D-*ribo*-C_6-phytosphingosines began with the selective halogenation (Scheme 2) of the methyl β-glycosides of D-GlcNAc (**4a**)[15b] and D-AllNAc (**4b**),[15a] respectively. When following a published procedure[19] by treating either triol **4a** or **4b** with triphenylphosphine (2 equiv) and carbon tetraiodide (1 equiv) in pyridine at room temperature, it was found that the reactions proceeded very sluggishly. After we raised the temperature to 50 °C, the reactions proceeded smoothly, and both reactions were complete within 5–6 h. The desired 6-iodo derivatives **5a** and **5b** were obtained in 74% and 71% yields, respectively.

However, due to the difficulty encountered in the separation of by-product (Ph_3PO), as well as the high cost associated with carbon tetraiodide, we concluded that the PPh_3/CI_4 iodination method was not suitable for multigram-scale syntheses. Alternatively, a two-step route, better suited to large-scale syntheses was pursued, and the transformations were carried out in a one-pot manner (Scheme 3). Thus treatment of **4a** and **4b** with an essentially stoichiometric amount of mesyl chloride at low temperature in



Scheme 1. Retrosynthetic plan of phytosphingosines.



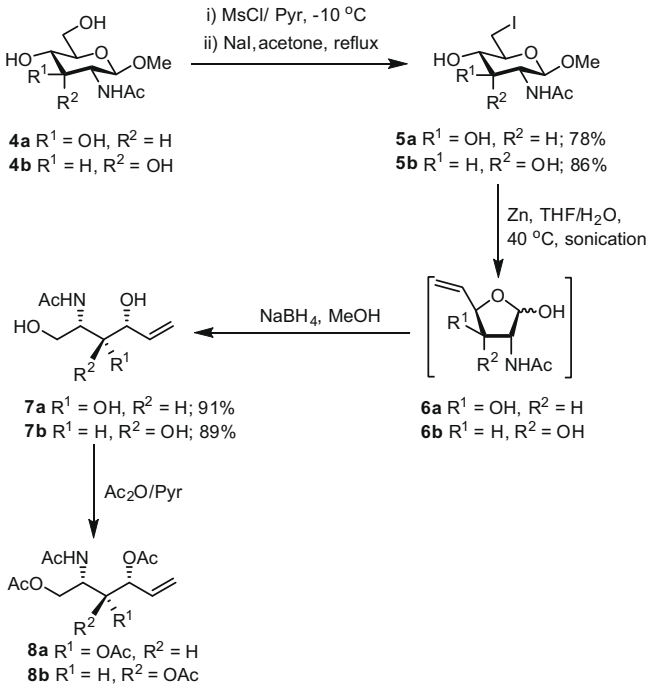
4a R^1 = OH, R^2 = H
4b R^1 = H, R^2 = OH

5a R^1 = OH, R^2 = H; 74%
5b R^1 = H, R^2 = OH; 71%

Scheme 2. One-step synthesis of 6-iodo derivatives **5a** and **5b**.

anhydrous pyridine afforded the corresponding 6-mesylates, and after removing the solvent, crude mesylates were reacted with sodium iodide in refluxing acetone to afford the 6-iodides **5a** and **5b**, respectively, in 78% and 86% yields over two steps and on a 5-g scale. Next, the zinc-mediated reductive ring-opening was investigated. The reactions of **5a** or **5b** with pre-activated zinc powder under sonication conditions[20] at 40 °C for 1–2 h afforded the desired aldehydes, which exist as the furanoses **6a** and **6b**. Direct reduction with $NaBH_4$ in MeOH afforded the corresponding D-*xylo*- (**7a**) and D-*ribo*-C6-phytosphingosines (**7b**) in excellent yields (91% for **7a** and 89% for **7b** over two steps). The procedure was successfully scaled to multigram quantities without complications. To facilitate the subsequent OCM reactions, both **7a** and **7b** were quantitatively converted to their peracetates **8a** and **8b**, which have better solubilities in dichloromethane, the common solvent used in OCM reactions.

With fully protected truncated phytosphingosines **8a** and **8b** in hand, their subsequent chain elongation was investigated (Scheme 4). The limited literature reporting the preparation of phytosphingosines revealed a drastic discrepancy in yields for the OCM reactions, ranging from 20% to 90%.[12] It is also known that the OCM reactions depend on the nature of the substrates, their protecting groups, and catalyst as well as reaction conditions.[21] We studied various conditions to enhance the efficiency in the elongation of the alkyl chain of substrates **8a** and **8b**. The results are summarized in Table 1. The metathesis was conducted in dichloromethane under refluxing conditions in the presence of 5 equiv of 1-tetradecene using Grubbs' second-generation catalyst



4a R^1 = OH, R^2 = H
4b R^1 = H, R^2 = OH

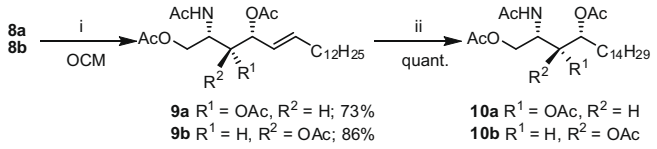
5a R^1 = OH, R^2 = H; 78%
5b R^1 = H, R^2 = OH; 86%

6a R^1 = OH, R^2 = H
6b R^1 = H, R^2 = OH

7a R^1 = OH, R^2 = H; 91%
7b R^1 = H, R^2 = OH; 89%

8a R^1 = OAc, R^2 = H
8b R^1 = H, R^2 = OAc

Scheme 3. Synthesis of truncated phytosphingosines **8a** and **8b**.



Scheme 4. OCM reactions with **8a** and **8b**.

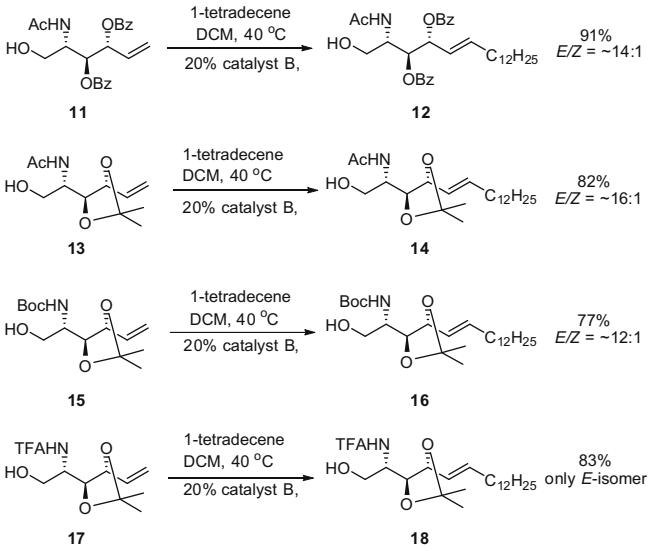
(catalyst B). It was found that, for substrate **8a**, only moderate yields (30–40%) were obtained by either prolonging the reaction time (5 days, entry 2) or even increasing the catalyst amount up to a 40% molar ratio (entry 3). After numerous trials, it was found that the manner of catalyst addition played a critical role in the outcome of the OCM reactions; for example, if the catalyst was added in one portion (protocol A, entries 1–3), the reaction never went to completion, and at least half of the starting material was recovered each time, leading to low yields. However, a dramatic improvement was observed when we added the catalyst in a portionwise manner (protocol B, entries 4–6). If the same amount of catalyst (20% molar ratios) was added in five portions at 2-h intervals, the yield of the desired product **9a** was improved to 86% as shown in entry 4; the reaction was quite clean, and only trace amounts of the starting material remained. Furthermore, by decreasing the amounts of catalyst to 10% molar ratio, the desired **9a** was still obtained in 78% yield (entry 5). Our results could be explained by the fact that only a small amount of catalyst was involved in the OCM reaction as most of the catalyst was quickly decomposed during the reaction;[22] therefore, a constant supply of catalyst to the reaction is the key to the success of OCM reactions. Using protocol B, truncated D-*ribo*-C_6-phytosphingosine **8b** was also smoothly reacted with 1-tetradecene to give **9b** in 73% yield (entry 6). Both 5,6-unstaturated C_{18}-phytosphingosines **9a** and **9b** were obtained with excellent *E*/*Z* selectivity, as only a trace amount of the *Z*-isomer was observed by ^{1}H NMR spectroscopy in the case of **9a** (*E*/*Z* = 19:1), and no *Z*-isomer was observed in the case of **9b**. The presence of the trans double bond at C-5/C-6 was unambiguously confirmed by the large ^{1}H NMR coupling constant (>15 Hz) between H-5 and H-6. The flexibility of our synthetic route is illustrated by converting the unsaturated phytosphingosines **9a** and **9b** to the saturated forms **10a** and **10b** in quantitative yields after a catalytic hydrogenation step. The spectroscopic and optical data of both **10a** and **10b** were in full agreement with those reported in the literature.[23]

The applicability of protocol B to other truncated structures[24] appears to be quite robust (**11**, **13**, **15,** and **17**, Scheme 5) and is compatible with substrates that contain protecting groups such as acetyl, benzoyl, acetonide, Boc, and TFA groups. The efficiency

Table 1
Studies on OCM chain elongations[a]

Entry	Substrates	Catalyst B (mol %)	Addition times (h)	Reaction protocol[b]	Yield[c] (%)
1	**8a**	20	18	A	36[d]
2	**8a**	40	72	A	41[d]
3	**8a**	20	120	A	32[d]
4	**8a**	20	18	B	86
5	**8a**	10	18	B	78
6	**8b**	20	18	B	73

[a] All reactions were heated to 40 °C with 1-tetradecene (5 equiv) added.
[b] Protocol A: catalyst B was added in one portion at the beginning of reactions; Protocol B: catalyst B was added in 5 portions every 2 h during the reactions.
[c] Isolated yields.
[d] Starting materials (49–55%) were recovered.



Scheme 5. Chain elongation of truncated compounds **11**, **13**, **15,** and **17** by OCM reaction.

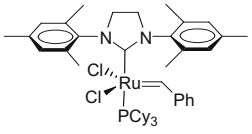
of the chain elongation was unaffected with good to excellent yields of the OCM products (**12**, **14**, **16,** and **18**) and in all cases with excellent *E*/*Z*-ratios (>12:1). In the case of the TFA-protected phytosphingosine (**17**), the *E*-isomer was obtained exclusively in 83% yield.

In summary, a general and flexible approach to C_6-phytosphingosines containing a terminal double bond was established using amino sugars as convenient starting materials. The alkyl chains of these truncated amino alcohols can be extended to desired lengths via a OCM reaction to afford 5,6-unsaturated phytosphingosines, which can also be converted to the saturated homologs by hydrogenation.

3. Experimental

3.1. General methods

All chemical reagents were used as supplied unless indicated. Solvents used in organic reactions were either distilled under an inert atmosphere, or purified by a solvent purification system by Innovative Technology, Inc. Unless otherwise noted, all reactions were carried out at rt, and non-hydrolytic reactions were performed under a positive pressure of argon. Solvents were removed between 20 and 40 °C (bath temperature) unless indicated. Molecular sieves were stored in an oven (>170 °C) and cooled in vacuo prior to use. Amberlite IR-120 resin (H^+) was used where acidic ion-exchange resin is indicated. Amberlite IR-400 (Cl^-) was treated with M NaOH (3×), followed by washing with MeOH (3 ×) to afford the basic ion-exchange resin. Analytical TLC was performed on Silica Gel 60-F_{254} with detection by quenching of fluorescence and/or by charring with 5% ethanolic sulfuric acid or with a cerium ammonium molybdate dip. Grubbs' second-generation catalyst employed in all olefin cross-metathesis has the following chemical structure.



Grubbs' second generation catalyst

3.2. Characterization

^{1}H NMR spectra were recorded at 400, 500, or 600 MHz, and ^{13}C NMR spectra were recorded at 125 MHz. First-order ^{1}H NMR chemical shifts are reported in δ (ppm) units using signals from residual solvents as reference or to internal acetone at δ 2.225 in the case of D_2O. ^{13}C NMR chemical shifts are referenced to internal solvent (δ_C 77.00, $CDCl_3$) or to external acetone at δ 31.07 in the case of D_2O. ^{1}H and ^{13}C NMR spectra were assigned with the assistance of COSY, HMQC, HMBC, TOCSY, and TROESY spectra as necessary. Electrospray-ionization mass spectra (ESIMS) were recorded on a TOF mass spectrometer. For high-resolution mass determination, spectra were obtained by voltage scan over a narrow range at a resolution of approximately 10^4. Optical rotations were determined for samples in a 10-cm cell at 22 ± 2 °C, and are reported in units of deg mL g^{-1} dm^{-1}.

3.3. Methyl 2-acetamido-2,6-dideoxy-6-iodo-β-D-glucopyranoside (5a)

3.3.1. Method A

To a solution of methyl 2-acetamido-2-deoxy-β-D-glucopyranoside[15b] **4a** (1.175 g, 5 mmol) and PPh_3 (3.93 g, 15 mmol) in anhyd pyridine (55 mL) was added portionwise CI_4 (3.9 g, 7.5 mmol) at 0 °C. The mixture was warmed to 40 °C and stirred for 5–6 h (monitored by TLC). The reaction was quenched by addition of MeOH (10 mL), and the mixture was concentrated and filtered. The filtrate was concentrated, and the mixture was separated by chromatography on silica gel using 3% MeOH in CH_2Cl_2 as eluent to give a pale-yellow solid residue. This residue was dissolved in MeOH (20 mL) and Dowex MR-3 mixed-bed ion-exchange resin (10 g) was added. The mixture was stirred at rt for 20 min, and the resin was filtered off. Subsequent concentration of the filtrate gave the desired compound **5a** as a white amorphous solid (1.24 g, 74%).

3.3.2. Method B

Methanesulfonyl chloride (1.6 mL, 20.6 mmol) was added dropwise to a solution of methyl 2-acetamido-2-deoxy-β-D-glucopyranoside **4a** (4.7 g, 20 mmol) in dry pyridine (150 mL) at −10 °C. The mixture was stirred at −10 °C for 18 h to form the intermediate 6-mesylate (R_f: 0.37, 5:1 CH_2Cl_2–MeOH). After concentration, the residue was redissolved in dry acetone (160 mL), and NaI (9 g, 60 mmol) was added. The mixture was stirred at reflux for 18 h. Filtration, followed by evaporation, gave a residue, which was subjected to silica gel chromatography using 3% MeOH in CH_2Cl_2 as eluent to afford crude **4a**, which was dissolved in MeOH (30 mL) and treated with Dowex MR-3 mixed-bed ion-exchange resin (10 g). After stirring at rt for 20 min, the resin was filtered off. Subsequent concentration of the filtrate afforded the desired compound **5a** as a white amorphous solid (5.4 g, 78%): R_f 0.59 (5:1 CH_2Cl_2–MeOH); $[\alpha]_D$ −2.2 (*c* 0.68, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ 4.34 (d, 1H, $J_{1,2}$ = 8.5 Hz, H-1), 3.63 (d, 1H, $J_{2,3}$ = 10.3 Hz, H-2), 3.61 (dd, 1H, $J_{6a,6b}$ = 10.7 Hz, H-6a), 3.46 (s, 3H, OCH_3), 3.44 (dd, 1H, $J_{3,4}$ = 8.6 Hz, H-3), 3.32 (dd, 1H, H-6b), 3.18 (dd, 1H, $J_{4,5}$ = 9.2 Hz, H-4), 3.10 (ddd, 1H, $J_{5,6b}$ = 7.4 Hz, $J_{5,6a}$ = 2.4 Hz, H-5), 1.98 (s, 3H, $NHCOCH_3$); ^{13}C NMR (125 MHz, CD_3OD): δ 173.8, 103.3, 76.6, 75.9, 75.7, 57.4, 57.0, 22.9, 6.4; HRESIMS: calcd for $C_9H_{16}INO_5Na$ ($M+Na^+$) *m/z* 367.9966; found, *m/z* 367.9970.

3.4. Methyl 2-acetamido-2,6-dideoxy-6-iodo-β-D-allopyranoside (5b)

3.4.1. Method A

To a solution of methyl 2-acetamido-2-deoxy-β-D-allopyranoside[15a] **4b** (235 mg, 1 mmol) in anhyd pyridine (10 mL) at 0 °C, PPh_3 (786 mg, 3 mmol) and CI_4 (780 mg, 2.5 mmol) were successively added in portions. The mixture was warmed to 40 °C and stirred for 5–6 h (the reaction was monitored by TLC). MeOH (2 mL) was added to quench the reaction. After concentration, the precipitate was filtered off, and the solvent was removed under reduced pressure. The resulting residue was purified by chromatography on silica gel using 3% MeOH in CH_2Cl_2 as eluent to give a pale-yellow solid residue that was dissolved in MeOH (5 mL) and treated with Dowex MR-3 mixed-bed ion-exchange resin (2 g). The mixture was stirred at rt for 20 min, and the resin was filtered off. Subsequent concentration of the filtrate gave the desired compound **5b** as a white amorphous solid (245 mg, 71%).

3.4.2. Method B

Methanesulfonyl chloride (1.23 mL, 16.2 mmol) was added dropwise to a solution of methyl 2-acetamido-2-deoxy-β-D-allopyranoside **4b** (3.47 g, 14.8 mmol) in dry pyridine (100 mL) at −30 °C. The mixture was stirred at −30 °C for 18 h to form the intermediate 6-mesylate (R_f: 0.31, 5:1 CH_2Cl_2–MeOH). After concentration, the residue was dissolved in dry acetone (120 mL). To the above solution, NaI (6.75 g, 45 mmol) was added, and the mixture was stirred at reflux for 18 h. After filtration, the solvent was removed. The residue was purified by silica gel chromatography using 3% MeOH in CH_2Cl_2 as eluent to give a solid residue which was dissolved in MeOH (20 mL) and treated with Dowex MR-3 mixed-bed ion-exchange resin (10 g) as above to afford the desired compound **5b** as a white amorphous solid (4.39 g, 86%): R_f 0.48 (10:1 CH_2Cl_2–MeOH); $[\alpha]_D$ −47.2 (*c* 1.12, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ 4.60 (d, 1H, $J_{1,2}$ = 8.6 Hz, H-1), 3.93 (dd, 1H, $J_{3,4}$ = 2.9 Hz, H-3), 3.77 (dd, 1H, $J_{2,3}$ = 2.8 Hz, H-2), 3.59 (dd, 1H, $J_{6a,6b}$ = 10.5 Hz, H-6a), 3.55 (ddd, 1H, $J_{5,6b}$ = 7.7 Hz, $J_{5,6a}$ = 2.4 Hz, H-5), 3.47 (s, 3H, OMe), 3.36 (dd, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 3.27 (dd, 1H, H-6b), 1.98 (s, 3H, $NHCOCH_3$); ^{13}C NMR (125 MHz, CD_3OD): δ 173.0, 101.2, 74.4, 72.6, 71.4, 56.9, 55.0, 22.6, 7.5; HRESIMS: calcd for $C_9H_{17}NO_5I$ ($M+H^+$) *m/z* 346.0146; found, *m/z* 346.0146. Anal. Calcd for $C_9H_{16}INO_5$: C, 31.32; H, 4.67; N, 4.06. Found: C, 31.85; H, 5.01; N, 4.00.

3.5. (2*S*,3*R*,4*R*)-2-Acetamidohex-5-ene-1,3,4-triol (7a)

To a solution of compound **5a** (2.40 g, 7 mmol) in a mixture of 4:1 THF–water (30 mL) was added freshly activated zinc powder (4.57 g, 70 mmol). The mixture was sonicated at 40–50 °C for 2 h and passed through a short silica gel pad and eluted with acetone. After concentration, the residue was dissolved in dry MeOH (20 mL), and $NaBH_4$ (1.32 g, 35 mmol) was added in portions at 0 °C. The reaction was allowed to continue from 0 °C to rt over 18 h, at the end of which time it was quenched by addition of HOAc (1 mL). After filtration through a short silica gel pad and concentration of the filtrate, the residue was purified by chromatography on silica gel using a gradient of 10–15% MeOH in CH_2Cl_2, affording the desired product **7a** as a white amorphous solid (1.2 g, 91%): R_f 0.46 (5:1 CH_2Cl_2–MeOH); $[\alpha]_D$ −5.5 (*c* 0.62, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ 5.90 (ddd, 1H, $J_{5,6t}$ = 17.1 Hz, $J_{5,6c}$ = 10.5 Hz, H-5), 5.29 (ddd, 1H, $J_{6t,6c}$ = 1.6 Hz, H-6t), 5.16 (ddd, 1H, H-6c), 4.02 (ddd, 1H, $J_{2,3}$ = 2.7 Hz, H-2), 3.96 (ddd, 1H, $J_{4,5}$ = 6.9 Hz, $J_{4,6}$ = 1.2 Hz, H-4), 3.67 (dd, 1H, $J_{3,4}$ = 7.1 Hz, H-3), 3.60 (dd, 1H, $J_{1a,1b}$ = 10.8 Hz, $J_{1a,2}$ = 6.9 Hz, H-1a), 3.52 (dd, 1H, $J_{1b,2}$ = 6.0 Hz, H-1b), 1.96 (s, 3H, $NHCOCH_3$); ^{13}C NMR (125 MHz, CD_3OD): δ 173.3, 138.9, 117.1, 74.8, 73.7, 62.8, 52.2, 22.9; HRESIMS: calcd for $C_8H_{15}NO_4Na$ ($M+Na^+$) *m/z* 212.0893; found, *m/z* 212.0895.

3.6. (2*S*,3*S*,4*R*)-2-Acetamidohex-5-ene-1,3,4-triol (7b)

To a solution of allopyranoside **5b** (345 mg, 1 mmol) in a mixture of 4:1 THF–water (5 mL) was added freshly activated zinc

powder (653 mg, 10 mmol). The mixture was sonicated at 40–50 °C for 2 h and then passed through a short silica gel pad, which was then washed with acetone. After concentration of the filtrate, the resulting residue was dissolved in dry MeOH (3 mL), and $NaBH_4$ (190 mg, 5 mmol) was added in portions at 0 °C. The mixture was stirred and allowed to warm to room temperature over 18 h. Then the reaction was quenched by addition of HOAc (0.5 mL). After filtration through a short silica gel pad and concentration of the filtrate, the residue was purified by silica gel chromatography using a gradient of 10–15% MeOH in CH_2Cl_2, affording the desired product **7b** as a white amorphous solid (168 mg, 89%): R_f 0.17 (10:1 CH_2Cl_2–MeOH); $[\alpha]_D$ +8.4 (*c* 0.63, MeOH); ^1H NMR (500 MHz, CD_3OD): δ 5.98 (ddd, 1H, $J_{5,6t}$ = 17.2 Hz, $J_{5,6c}$ = 10.5 Hz, H-5), 5.27 (ddd, 1H, $J_{6t,6c}$ = 1.7 Hz, H-6t), 5.17 (ddd, 1H, H-6c), 4.08 (ddd, 1H, $J_{4,5}$ = 5.5 Hz, $J_{4,6}$ = 1.4 Hz, H-4), 4.02 (ddd, 1H, $J_{2,3}$ = 6.0 Hz, H-2), 3.76 (dd, 1H, $J_{1a,1b}$ = 11.3 Hz, $J_{1a,2}$ = 4.3 Hz, H-1a), 3.71 (dd, 1H, $J_{1b,2}$ = 5.7 Hz, H-1b), 3.64 (dd, 1H, $J_{3,4}$ = 5.2 Hz, H-3), 1.96 (s, 3H, $NHCOCH_3$); ^{13}C NMR (125 MHz, CD_3OD): δ 173.2 138.7, 116.5, 75.4, 74.8, 62.0, 53.8, 49.5, 22.8; HRESIMS: calcd for $C_8H_{15}NO_4Na$ (M+Na^+) *m/z* 212.0893; found, *m/z* 212.0891.

3.7. (2*S*,3*R*,4*R*)-2-Acetamido-1,3,4-tri-*O*-acetylhex-5-ene-1,3,4-triol (8a)

To a solution of compound **7a** (190 mg, 1 mmol) in dry pyridine (2 mL), Ac_2O (0.15 mL) was added dropwise. The mixture was stirred at rt for 18 h and diluted with CH_2Cl_2, washed with water and brine, and dried over anhyd Na_2SO_4. Removal of solvent provided the pure target product **8a** as a colorless syrup (306 mg, 97%): R_f 0.18 (1:4 hexane–EtOAc); $[\alpha]_D$ −19.2 (*c* 2.4, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 5.78 (ddd, 1H, $J_{5,6t}$ = 17.1 Hz, $J_{5,6c}$ = 10.5 Hz, H-5), 5.69 (d, 1H, $J_{NH,2}$ = 9.5 Hz), 5.39 (ddd, 1H, $J_{4,5}$ = 6.3 Hz, $J_{4,6}$ = 1.1 Hz, H-4), 5.37 (d, 1H, H-6t), 5.34 (d, 1H, H-6c), 5.19 (dd, 1H, $J_{3,4}$ = 7.3 Hz, H-3), 4.55 (ddd, 1H, $J_{2,3}$ = 3.5 Hz, H-2), 4.01 (dd, 1H, $J_{1a,1b}$ = 11.3 Hz, $J_{1a,2}$ = 6.3 Hz, H-1a), 3.97 (dd, 1H, $J_{1b,2}$ = 5.9 Hz, H-1b), 2.10 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.02 (s, 3H, $NHCOCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 169.8, 169.7, 169.6, 131.3, 120.6, 73.0, 72.0, 62.9, 47.5, 23.3, 20.9, 20.7, 20.6; HRESIMS: calcd for $C_{14}H_{21}NO_7Na$ (M+Na^+) *m/z* 338.1210; found, *m/z* 338.1208.

3.8. (2*S*,3*R*,4*R*,5*E*)-2-Acetamido-1,3,4-tri-*O*-acetyloctadec-5-ene-1,3,4-triol (9a)

To a solution of compound **8a** (28 mg, 0.09 mmol) and 1-tetradecene (0.112 mL, 0.445 mmol) in dry CH_2Cl_2 (2 mL), Grubbs' second-generation catalyst (20%, 15.3 mg) was added portionwise (protocol B) at reflux. The reaction was continued for 18 h under gentle reflux. After concentration, the residue was chromatographed on silica gel using 1:1 to 1:2 hexane–EtOAc as eluent to yield the desired compound **9a** as a white amorphous solid (37 mg, 86%, *E*/*Z* = 19:1): R_f 0.41 (1:5 hexane–EtOAc); ^1H NMR (500 Hz, $CDCl_3$): δ 5.82 (ddd, 1H, $J_{6,7a}$ = 6.7 Hz, $J_{6,7b}$ = 4.1 Hz, H-6), 5.69 (d, 1H, $J_{NH,H\text{-}2}$ = 9.5 Hz, NH), 5.32–5.38 (m, 2H, $J_{5,6}$ = 14.7 Hz, H-5 and H-4), 5.17 (dd, 1H, *J* = 7.4 Hz, *J* = 3.4 Hz, H-3), 4.52 (dddd, 1H, *J* = 7.8 Hz, *J* = 3.2 Hz, H-2), 3.94–4.02 (dd, 2H, $J_{1a,1b}$ = 11.3 Hz, *J* = 6.4 Hz, H-1a and H1b), 2.09 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 2.02 (s, 3H, $NHCOCH_3$), 2.02 (m, 2H, alkane CH_2), 1.32–1.40 (d, 2H, *J* = 6.1 Hz, alkane CH_2), 1.20–1.32 (m, 18H, alkane CH_2), 0.88 (t, 3H, *J* = 6.7 Hz, alkyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 169.8, 169.8, 169.5, 138.9, 122.6, 73.2, 72.3, 62.9, 47.5, 32.3, 31.9, 29.7, 29.6, 29.6, 29.6, 29.4, 29.3, 29.2, 28.6, 23.2, 22.7, 21.0, 20.7, 20.6, 14.1; HRESIMS: calcd for $C_{26}H_{45}NO_7Na$ (M+Na^+) *m/z* 506.3088; found, *m/z* 506.3089.

3.9. (2*S*,3*S*,4*R*,5*E*)-2-Acetamido-1,3,4-tri-*O*-acetyloctadec-5-ene-1,3,4-triol (9b)

Triol **7b** (28 mg, 0.148 mmol) was dissolved in dry pyridine (2 mL), and Ac_2O (0.15 mL) was added dropwise. The mixture was stirred at rt for 18 h. Then the solution was diluted with CH_2Cl_2, and the organic phase was washed with water and brine and dried over anhyd Na_2SO_4. Removal of solvent gave a colorless syrup **8b** that was redissolved in dry CH_2Cl_2 (3 mL) followed by addition of 1-tetradecene (0.184 mL, 0.73 mmol). To the resulting mixture, Grubbs' second-generation catalyst (20%, 25 mg) was added in four portions (protocol B) under reflux. The reaction was continued for 18 h at gentle reflux. The mixture was concentrated and purified by chromatography on silica gel using 1:1 to 1:2 hexane–EtOAc as eluent to yield the desired compound **9b** as a white amorphous solid (52 mg, 73%): R_f 0.53 (1:5 hexane–EtOAc); $[\alpha]_D$ +11.4 (*c* 0.44, $CHCl_3$); ^1H NMR (400 Hz, $CDCl_3$): δ 6.05 (d, 1H, $J_{NH,\ H\text{-}2}$ = 9.5 Hz, NH), 5.83 (ddd, 1 H, $J_{6,7}$ = 6.8 Hz, 6.8 Hz, H-6), 5.45 (dd, 1H, $J_{5,6}$ = 15.7 Hz, H-5), 5.34 (dd, 1H, $J_{4,5}$ = 8.0 Hz, H-4), 5.14 (dd, 1H, $J_{3,4}$ = 3.4 Hz, H-3), 4.45 (dddd, 1H, $J_{NH,H\text{-}2}$ = 10.8 Hz, $J_{2,3}$ = 8.0 Hz, H-2), 4.30 (dd, 1H, $J_{1a,1b}$ = 11.6 Hz, $J_{1a,2}$ = 4.6 Hz, H-1a), 3.99 (dd, 1H, $J_{1b,2}$ = 3.3 Hz, H-1b), 2.08 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.03 (s, 3H, $NHCOCH_3$), 2.02 (m, 2H, alkane CH_2), 1.34–1.42 (d, 2H, *J* = 6.1 Hz, alkane CH_2), 1.20–1.34 (m, 18H, alkane CH_2), 0.88 (t, 3H, *J* = 6.7 Hz, alkyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 170.3, 170.0, 169.4, 138.9, 121.8, 74.0, 72.1, 62.8, 47.8, 32.4, 31.9, 29.7, 29.6, 29.6, 29.6, 29.4, 29.3, 29.2, 28.8, 23.4, 22.7, 21.1, 20.8, 20.7, 14.1; HRESIMS: calcd for $C_{26}H_{45}NO_7Na$ (M+Na^+) *m/z* 506.3088; found, *m/z* 506.3088.

3.10. (2*S*,3*R*,4*R*)-2-Acetamido-1,3,4-tri-*O*-acetyloctadecane-1,3,4-triol (D-*xylo*-phytosphingosine tetraacetate) (10a)

To a solution of compound **9a** (20 mg, 0.04 mmol) in EtOAc (2 mL) was added a catalytic amount of palladium hydroxide-on-charcoal (15 mg). The mixture was stirred at rt under an atmosphere of hydrogen for 18 h. After filtration, the filtrate was concentrated, and the residue was dried under vacuum to provide the desired product **10a** as a white amorphous solid in quantitative yield: R_f 0.45 (1:4 hexane–EtOAc); $[\alpha]_D$ +6.0 (*c* 0.62, $CHCl_3$); {lit.[23b] $[\alpha]_D$ +6.3 (*c* 0.86, $CHCl_3$)}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.71 (d, 1H, $J_{NH,H\text{-}2}$ = 9.5 Hz, NH), 5.16 (dd, 1H, $J_{3,4}$ = 6.5 Hz, H-3), 5.06 (ddd, 1H, $J_{4.5}$ = 6.6 Hz, H-4), 4.53 (dddd, $J_{2,3}$ = 4.4 Hz, H-2), 4.05 (dd, 1H, $J_{1a,1b}$ = 11.4 Hz, $J_{1a,2}$ = 6.0 Hz, H-1a), 4.01 (dd, 1H, $J_{1b,2}$ = 5.7 Hz, H-1b), 2.09 (s, 3H, $COCH_3$), 2.06 (s, 6H, $COCH_3$), 2.02 (s, 3H, $NHCOCH_3$), 1.55–1.64 (m, 2H, alkane CH_2), 1.20–1.35 (m, 24H, alkane CH_2), 0.88 (t, 3H, *J* = 6.7 Hz, alkyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.5, 170.1, 169.8, 72.3, 71.9, 62.9, 48.0, 31.9, 30.5, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 24.8, 23.2, 22.7, 20.9, 20.7, 20.6, 14.1; HRESIMS: calcd for $C_{26}H_{47}NO_7Na$ (M+Na^+) *m/z* 508.3245; found, *m/z* 508.3246.

3.11. (2*S*,3*S*,4*R*)-2-Acetamido-1,3,4-tri-*O*-acetyloctadecane-1,3,4-triol (D-*ribo*-phytosphingosine tetraacetate, 10b)

To a solution of compound **9b** (15 mg, 0.03 mmol) in EtOAc (2 mL) was added a catalytic amount of palladium hydroxide-on-charcoal (12 mg). The mixture was stirred under an atmosphere of hydrogen at rt for several hours. After filtration, the filtrate was concentrated, and the residue was dried under vacuum to afford the desired product **10b** as a white amorphous solid (13.8 mg, 92%): R_f 0.58 (1:5 hexane–EtOAc); $[\alpha]_D$ +25.8 (*c* 1.4, $CHCl_3$); {lit.[23a] $[\alpha]_D$ +27.8 (*c* 0.8, $CHCl_3$), lit.[8f] $[\alpha]_D$ +26.5 (*c* 0.84, $CHCl_3$), lit.[25] $[\alpha]_D$ +26.2 (*c* 2.0, $CHCl_3$)}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.91 (d, 1H, $J_{NH,H\text{-}2}$ = 9.4 Hz, NH), 5.10 (dd, 1H, $J_{3,4}$ = 3.1 Hz, H-3), 4.94 (dt, 1H,

$J_{4,5a}$ = 3.2 Hz, $J_{4,5b}$ = 9.9 Hz, H-4), 4.48 (dddd, 1H, $J_{2,3}$ = 8.2 Hz, H-2), 4.29 (dd, 1H, $J_{1a,1b}$ = 11.7 Hz, $J_{1a,2}$ = 5.0 Hz, H-1a), 4.01 (dd, 1H, $J_{1b,2}$ = 3.1 Hz, H-1b), 2.08 (s, 3H, $COCH_3$), 2.05 (s, 6H, $COCH_3$), 2.03 (s, 3H, $NHCOCH_3$), 1.55–1.64 (m, 2H, alkyl CH_2), 1.20–1.35 (m, 24H, alkyl CH_2), 0.88 (t, 3H, J = 6.7 Hz, alkyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 170.8, 170.0, 169.7, 73.0, 72.1, 62.8, 47.7, 31.9, 29.7, 29.6, 29.6, 29.6, 29.5, 29.3, 29.3, 28.2, 25.5, 23.3, 22.7, 21.0, 20.7, 20.7, 14.1; HRESIMS: calcd for $C_{26}H_{47}NO_7Na$ (M+Na^+) *m/z* 508.3245; found, *m/z* 508.3247.

3.12. (2*S*,3*S*,4*R*,5*E*)-2-Acetamido-3,4-di-*O*-benzoyloctadec-5-ene-1,3,4-triol (12)

To a solution of compound **11** (50 mg, 0.126 mmol) and 1-tetradecene (0.16 mL, 0.63 mmol) in dry CH_2Cl_2 (5 mL), Grubbs' second-generation catalyst (20%, 26.7 mg) was added in four portions (protocol B) under reflux. The reaction was continued under gentle reflux for 18 h (TLC showed that almost all starting material was consumed). Concentration and chromatography of the residue on silica gel using 1:5 hexane–EtOAc as eluent gave the target product **12** as a white amorphous solid (65 mg, 91%, *E*/*Z* = ~14:1): R_f 0.48 (1:5 hexane–EtOAc). ^1H NMR (600 MHz, $CDCl_3$): δ 8.07 (d, 2H, J = 7.2 Hz, ArH), 7.96 (d, 2H, J = 10.8 Hz, ArH), 7.64 (t, 1H, J = 7.4 Hz, ArH), 7.48–7.54 (m, 3H, ArH), 7.38 (t, 2H, J = 7.7 Hz, ArH), 6.30 (d, 1H, $J_{NH,H\text{-}2}$ = 9.2 Hz, NH), 6.03 (ddd, 1H, $J_{5,6}$ = 14.3 Hz, $J_{6,7}$ = 6.9 Hz, 7.4 Hz, H-6), 5.74–5.82 (m, 2H, H-5 and H-4), 5.41 (dd, 1H, J = 9.1 Hz, 2.5 Hz, H-3), 4.39 (m, 1H, H-2), 3.69 (dd, 1H, $J_{1a,1b}$ = 12.3 Hz, $J_{1a,2}$ = 2,5 Hz, H-1a), 3.64 (dd, 1H, $J_{1b,2}$ = 2.9 Hz, H-1b), 2.15 (q, 2H, J = 7.2 Hz, H-7 or =CHCH_2), 2.1 (s, 3H, $NHCOCH_3$), 1.38–1.44 (m, 2H, alkane CH_2), 1.20–1.32 (m, 18H, alkane CH_2), 0.88 (t, 3H, J = 7.1 Hz, alkyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 167.2, 165.5, 138.6, 133.9, 133.1, 130.0, 129.9, 129.7, 129.7, 129.0, 128.7, 128.6, 128.4, 122.0, 61.4, 50.3, 32.6, 31.9, 29.7, 29.6, 29.6, 29.4, 29.3, 29.3, 29.2, 28.9, 23.5, 22.7, 14.1; HRESIMS: calcd for $C_{34}H_{47}NO_6Na$ (M+Na^+) *m/z* 588.3296; found, *m/z* 588.3297.

3.13. (2*S*,3*S*,4*R*,5*E*)-2-Acetamido-3,4-*O*-isopropylideneoctadec-5-ene-1,3,4-triol (14)

To a solution of compound **13** (60 mg, 0.26 mmol) and 1-tetradecene (0.33 mL, 1.3 mmol) in dry CH_2Cl_2 (9 mL), Grubbs' second-generation catalyst (20%, 44 mg) was added in four portions (protocol B) under reflux. The reaction was continued for 18 h under gentle reflux (TLC showed that almost all starting material had disappeared). Concentration, followed by chromatography of the residue on silica gel using 1:5 hexane–EtOAc as eluent provided the target product **14** as a white amorphous solid (85 mg, 82%, *E*/*Z* = ~16:1): R_f 0.22 (1:5 hexane–EtOAc). ^1H NMR (500 MHz, $CDCl_3$): δ 5.96 (d, 1H, $J_{NH,H\text{-}2}$ = 8.2 Hz, NH), 5.84 (dt, 1H, $J_{6,7}$ = 6.8 Hz, H-6), 5.50 (ddd, 1H, $J_{5,6}$ = 15.3 Hz, H-5), 4.67 (dd, 1H, $J_{4,5}$ = 7.3 Hz, H-4), 4.24 (dd, 1H, $J_{3,4}$ = 6.0 Hz, H-3), 4.03 (dddd, 1H, $J_{2,3}$ = 6.3 Hz, H-2), 3.90 (dd, 1H, $J_{1a,1b}$ = 11.5 Hz, $J_{1a,2}$ = 3.5 Hz, H-1a) 3.68 (dd, 1H, $J_{1b,2}$ = 3.5 Hz, H-1b), 2.02–2.08 (m, 2H, H-7 or =CHCH_2), 1.98 (s, 3H, $NHCOCH_3$), 1.50 (s, 3H, $C(CH_3)_2$), 1.36 (s, 3H, $C(CH_3)_2$), 1.20–1.40 (m, 20H, alkane CH_2), 0.88 (t, 3H, J = 6.8 Hz, alkyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8 (C=O), 139.1, 124.2, 108.5, 78.8, 63.1, 50.7, 32.4, 31.9, 29.7, 29.6, 29.6, 29.6, 29.5, 29.3, 29.3, 29.0, 27.3, 24.8, 23.4, 22.7, 14.1; HRESIMS: calcd for $C_{23}H_{43}NO_4Na$ (M+Na^+) *m/z* 420.3084; found, *m/z* 420.3085.

3.14. (2*S*,3*S*,4*R*,5*E*)-2-*N*-(*tert*-Butoxycarbonyl)amino-3,4-*O*-isopropylideneoctadec-5-ene-1,3,4-triol (16)

To a solution of compound **15** (70 mg, 0.244 mmol) and 1-tetradecene (0.32 mL, 12.6 mmol) in dry CH_2Cl_2 (10 mL), Grubbs' second-generation catalyst (20%, 41.4 mg) was added in four portions (protocol B) under reflux. The reaction was continued for 18 h under gentle reflux. After concentration, the residue was purified by chromatography on silica using 4:1 hexane–EtOAc as eluent to afford the target product **16** as a white amorphous solid (85 mg, 77%, *E*/*Z* = ~12:1): R_f 0.34 (2:1 hexane–EtOAc). ^1H NMR (600 MHz, $CDCl_3$): δ 5.83 (dt, 1H, $J_{6,7}$ = 6.8 Hz, H-6), 5.50 (dd, 1H, $J_{5,6}$ = 15.3 Hz, H-5), 4.93 (s, br, 1H, NH), 4.65 (dd, 1H, $J_{4,5}$ = 7.2 Hz, H-4), 4.19 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 6.3 Hz, H-3), 3.86 (dd, 1H, $J_{1a,1b}$ = 11.0 Hz, $J_{1a,2}$ = 3.0 Hz, H1a), 3.70 (dd, 2H, J = 9.3 Hz, J = 3.2 Hz, H-2 and H1b), 2.06 (t, 2H, J = 7.0 Hz, =CHCH_2), 1.49 (s, 3H, $C(CH_3)_2$), 1.36 (s, 3H, $C(CH_3)_2$), 1.44 (s, 9H, $C(CH_3)_3$), 1.20–1.40 (m, 20H, alkane CH_2), 0.88 (t, 3H, J = 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 136.9, 124.2, 108.5, 78.9, 78.7, 63.5, 51.6, 32.5, 31.9, 29.7, 29.6, 29.6, 29.6, 29.5, 29.5, 29.3, 29.3, 29.0, 28.4, 27.4, 25.0, 22.7, 14.1; HRESIMS: calcd for $C_{26}H_{49}NO_5Na$ (M+Na^+) *m/z* 478.3503; found, *m/z* 478.3507.

3.15. (2*S*,3*S*,4*R*,5*E*)-3,4-*O*-Isopropylidene-2-trifluoroacetamido-octadec-5-ene-1,3,4-triol (18)

To a solution of compound **17** (40 mg, 0.14 mmol) and 1-tetradecene (0.18 mL, 0.7 mmol) in dry CH_2Cl_2 (5 mL), Grubbs' second-generation catalyst (20%, 23.7 mg) was added in four portions (protocol B) under reflux. The reaction was continued for 18 h under gentle reflux. Concentration, followed by chromatography of the residue on silica gel (4:1 hexane–EtOAc), afforded the target product **18** as a white amorphous solid (53 mg, 83%): R_f = 0.33 (2:1 hexane–EtOAc); $[\alpha]_D$ −4.06 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 6.79 (d, 1H, $J_{NH,H\text{-}2}$ = 8.2 Hz, NH), 5.85 (dt, 1H, $J_{6,7}$ = 6.7 Hz, H-6), 5.44 (dd, 1H, $J_{5,6}$ = 15.3 Hz, H-5), 4.70 (dd, 1H, $J_{4,5}$ = 7.3 Hz, H-4), 4.27 (dd, 1H, $J_{3,4}$ = 6.5 Hz, H-3), 4.09 (ddd, 1H, $J_{2,3}$ = 6.0 Hz, H-2), 4.00 (dd, $J_{1a,1b}$ = 11.5 Hz, $J_{1a,2}$ = 2.7 Hz, H-1a), 3.70 (dd, 1H, $J_{1b,2}$ = 3.4 Hz, H-1b), 2.04 (q, 2H, J = 7.1 Hz, =CCH_2), 1.51 (s, 3H, $C(CH_3)_2$), 1.38 (s, 3H, $C(CH_3)_2$), 1.20–1.40 (m, 20H, alkane CH_2), 0.88 (t, 3H, J = 6.8 Hz, alkyl CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.5, 137.8, 123.3, 115.6, 108.9, 78.6, 77.7, 62.0, 50.8, 32.3, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.3, 28.8, 27.3, 24.8, 22.7, 14.1; HRESIMS: calcd for $C_{23}H_{40}F_3NO_4Na$ (M+Na^+) *m/z* 474.2802; found, *m/z* 474.2804. Anal. Calcd for $C_{23}H_{40}F_3NO_4$: C, 61.18; H, 8.93; N, 3.10. Found: C, 61.42; H, 8.72; N, 3.28.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2009.07.007.

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